Chapter 5 - HUMAN HEALTH EFFECTS AND TOXICOLOGY

A. Introduction

All mercurial compounds are toxic and they affect many organ systems both during pre-natal and post-natal development and in adulthood. Mercury compounds are neurotoxic. Some are immunologically active. The main toxicity stems from the binding of mercury to sulfhydryl groups of enzymes and other proteins, thereby disrupting their structure and function. This interferes with basic cellular processes and damages or kills cells. The different forms of mercury differ in their ability to penetrate membranes and gain access to organs such as the brain. It is generally the neurotoxicity, that is of greatest importance, although some forms of mercury damage the kidneys and some compounds are highly corrosive to skin and mucous membranes.

Overall, the toxicity to the developing nervous system of the fetus is considered the most critical endpoint. However, recent evidence suggests that cardiovascular effects can occur in adults at comparably low doses. It will be necessary to follow the emergence of additional studies in the future. The toxicology of mercury compounds has been reviewed by ATSDR (1999a).

B. Methylmercury Neurodevelopmental Toxicity

The following is presented as a brief introduction to and summary of the current understanding of the toxicology of methylmercury (MeHg). Significant uncertainties remain, and a full presentation of the available data and their accompanying uncertainties is beyond the scope of this report. More complete discussion and analysis can be found in several recent publications:

- The National Research Council's *Toxicological Effects of Methylmercury*, (NRC 2000);
- The US EPA's *Mercury Report to Congress* (USEPA 1997c and 1997e);
- The ATSDR 1999 update of its *Toxicological Profile for Mercury* (ATSDR 1999a) and
- The report of the National Institute of Environmental Health Sciences' Workshop on *Scientific Issues Relevant to Assessment of Health Effects from Exposure to Methylmercury (NIEHS 1998)*

Entire issues of journals have been devoted to methylmercury toxicity (see, for example, the winter 1995 issue of Neurotoxicology, Cramer 1995), although the toxicity of methylmercury has long been known.

1. Minamata Disease

Although it has long been known that high level methylmercury exposure resulted in profound impacts on central nervous system function in humans, more recent investigations of animals (Newland and Paletz 2000a; Newland and Rasmussen 2000) and populations with lower level exposure (Rice 2000), have identified specific functional effects, for example, sensory effects and subtle changes in response to conditioning paradigms, rather than memory. Performance decrements were found at doses of 10μg/kg/day, while visual-evoked potential changes and ataxia occurred at doses two orders of magnitude higher (Newland and Paletz 2000).

Because of epidemics of widespread poisoning in Minamata in the 1950's and later in Nigata, Japan, MeHg was one of the first environmental contaminants to be recognized with the potential to adversely affect large numbers of people with relatively low levels of exposure. For many years, fisher families had suffered a strange debilitating disease, which was finally recognized as methylmercury poisoning (Kurland et al. 1960). These epidemics were followed by a mass poisoning in Iraq in 1971-1972 when people became sick after ingesting grain that had been treated with mercurial pesticide. In each of these cases, a range of neurological effects, reflecting damage to the central nervous system, was seen in the exposed populations of adults and older children. The severity of the effects were closely linked to the total dose, and ranged from paresthesias (pins and needles), to impairment of speech and gait, deafness, blindness, coma and even death.

In both the Japanese epidemics (where exposure was from mercury-contaminated fish) and the Iraq epidemic (where exposure was from grain treated with a mercurial fungicide), infants born to mothers with high mercury levels suffered qualitatively different effects than their mothers. These involved the central nervous system and included mental retardation, cerebral palsy, and severe delays in the attainment of developmental milestones (e.g., sitting, standing, walking, and talking). This syndrome became known as Congenital Minamata Disease. Data suitable for developing an understanding of dose-response were gathered from a subset of the Iraq cohort. Maternal exposure during pregnancy was estimated by analyzing mercury levels in segments of maternal hair that grew during the MeHg poisoning period. Data on adverse effects was collected from clinical neurological examinations and from maternal recall of developmental milestones.

Based on an analysis of the Iraqi data, the USEPA calculated a benchmark hair concentration for MeHg (lower 95% confidence interval on the concentration corresponding to a 10% response rate) of 11 ppm (US EPA 1995b). This hair concentration was converted to an estimate of average daily intake of 1.1 : g /kg/day by use of a pharmacokinetic model. An overall uncertainty factor adjustment of 10, addressing inter-individual variability and lack of complete data on other possible adverse effects, was applied to this dose to yield the current Reference Dose (RfD) for MeHg of 0.1 : g /kg/day.

Significant uncertainties in the design and interpretation of the Iraqi data have been identified. Comparison of the occurrence of developmental delays in the Iraqi population to those in populations with comparable mercury exposures resulting from fish consumption rather than from the consumption of treated grain (over a relatively shorter period of time), did not confirm the developmental delays predicted from the dose-response analysis of the Iraqi data (NRC, 2000).

The adverse neurological developmental effects recorded in the Iraqi study were all classifiable as clinical effects. That is, they are conditions that can be recognized as abnormal by the individual or detected by a clinician evaluating that individual. In contrast, sub-clinical effects are those that would result in a decrement in function but would not be recognized as abnormal by the individual, nor would they be detectable without specialized tests. It is a typical feature of dose-response curves that subclinical effects occur at exposures below those that result in clinical effects. Unlike other adverse outcomes, such as cancer for instance, in which a tumor either is or is not present, neurological function operates on a continuous scale. An example of this is IQ performance. An individual, whose IQ performance is within the range of normal, could still have a lower IQ score than he or she would have had in the absence of exposure to MeHg.

It is possible to compare the IQ scores of groups of children with high in-utero exposure to mercury to children with low in-utero exposure. If MeHg exposure resulted in sub-clinical reduction of IQ performance, such effects might be expected to be manifested as differences in mean IQ scores between such groups of children. Such considerations underlie the current guidance for identifying and controlling low-level lead exposures in children (ATSDR 1999b).

The studies discussed below, which followed the Iraqi study, investigated populations that are exposed to MeHg through fish consumption. As such, they are more appropriate for consideration of exposures in the US (and NJ). These populations were not overtly poisoned and no cases of Congenital Minamata Disease occurred. They are discussed in more detail because they provide the rationale for attempts to reduce mercury contamination and exposure. For comparison, hair concentrations of mercury in the US are typically less than 1 ppm.

Adverse effects that may occur in the study populations described below are determined on the basis of epidemiological studies examining the possible association between MeHg exposure during gestation and decreased performance on specific developmental neurological and neurobehavioral tests. Such associations are investigated after controlling for other potential determinants of performance. These include birth weight, breastfeeding, income, ethnicity, maternal education, maternal smoking, alcohol consumption, general health status, nutritional status, etc. The determination of an association is, therefore, based on a statistical analysis, which attempts to isolate the specific influence of MeHg from among other possible determinants of test outcome.

2. New Zealand Study

Subsequent to the Iraqi poisoning, a study was undertaken in New Zealand focusing on children of mothers who consumed fish (mostly shark) (Kjellstrøm et al. 1986; 1989). There were no known cases of clinical effects attributed to MeHg exposure in this population. Approximately 90% of the mothers had hair mercury levels of 6-12 ppm during pregnancy. Maternal hair mercury levels >10 ppm and possibly those in the range of 6-10 ppm were found to result in decrements in tests of cognitive ability (IQ), verbal ability and motor function when other influences (e.g., ethnicity) were taken into account. A recent re-analysis of these data (Crump et al. 1998) suggested benchmark concentrations in the same range as those derived by the USEPA from the Iraqi data.

3. Seychelles Study

An ongoing study in the Seychelles Islands (in the Indian Ocean, off the eastern coast of Africa) has been following a cohort of about 700 children (main cohort) whose mothers were exposed to MeHg from fish consumption during pregnancy. The Seychelles Islands were chosen for study because fish is a staple of the diet in that population. The median maternal hair mercury concentration is about 6 ppm with about 20% >12 ppm. The children were evaluated at 6, 19, 29, and 66 months of age. Separate pilot studies of 789 children of mixed ages (from <10 weeks to >2 years old), and a group of 247 children at 66-months old were also conducted (Davidson et al. 1998). In the main cohort, a significant relationship was observed between maternal MeHg exposure and decreased activity level in boys. For all other tests, including intelligence, psychomotor function, visual attention, visual recognition, gross neurological function, and general developmental competency (Denver Developmental Screening Test), no association between maternal exposure and test outcome was observed. In the mixed age pilot study, maternal hair mercury above 12 ppm was associated with an increase in combined abnormal and questionable performance. In the 66-month pilot study,

maternal hair mercury was clearly associated only with decreased auditory comprehension, but not eight other tests of intelligence, language, and motor skills. Given the large number of separate tests administered in this study overall, it is not clear if the few observations of associations reflect true associations, or if they occurred by chance alone. In general, however, the Seychelles study has not found a strong relationship between maternal MeHg exposure and impaired neurologic performance in children. The authors generally consider this a "negative study".

4. Faroe Island Study

Another major ongoing prospective study of children is being conducted on the Faroe Islands (located in the North Atlantic between Scotland and Iceland, and politically part of Denmark) (Weihe et al. 1996). Here, too, people eat large quantities of fish, frequently supplemented by the meat of Pilot Whale. A cohort of about 900 mothers and children is being followed and the children have been tested at 7 years old. Exposure was measured both as maternal hair mercury concentration, and as fetal cord blood mercury concentration (obtained at delivery). The median maternal hair mercury concentration was 4.3 ppm with 15% >10 ppm (Grandjean et al. 1997).

Pilot Whale has high concentrations of PCBs, as well as MeHg. Since PCBs are also known to adversely affect neurological development, the interpretation of the results from this study is somewhat complicated. In whales, MeHg tends to be found mostly in muscle tissue, while PCBs tend to be found in blubber. Some Faroese eat whale blubber and others do not. To some extent, this permits statistical separation of MeHg and PCB exposure and effects on a population basis.

In eight of 20 neuropsychological tests (including language, attention, and memory), decreased test performance was associated with cord blood mercury concentration (similar and only slightly weaker associations were also observed with maternal hair mercury concentration). In four of these eight tests, PCBs were also associated with decreased test performance. However, statistical analysis allowed the researchers to determine that even if PCBs are contributing to the impairment, there was an independent effect of MeHg on performance. The types of functions affected by MeHg appear to be generally comparable to those found in the New Zealand study (see above).

The National Institute of Environmental Health Sciences (NIEHS) held a workshop in 1998 to assess the current studies relating to the human health impact of MeHg. The NIEHS workshop (NIEHS 1998) concluded that "Results from the Faroes and Seychelles studies are credible and provide valuable insights into the potential health effects of methylmercury."

The recent NRC (2000) report noted the similarities in both types of adverse responses and in the quantitative dose-response relationship between the Faroes and New Zealand studies. That report investigated several possible reasons for the differences observed between these two positive studies and the negative Seychelles study. These include:

- different types of exposure measurements (hair vs. blood);
- different types of tests;
- different ages at testing;
- the potential influence of PCBs and other exposures;
- different fish consumption patterns;
- random statistical chance; and
- dietary and nutritional factors.

However, with the possible exception of statistical power, none of these possibilities appears to provide a sufficient explanation for these differences. The NRC committee concluded that the two positive studies provided a credible basis for the derivation of a Reference Dose (RfD), and identified the Boston Naming Test (a measure of verbal intelligence) in the Faroes study as the most appropriate basis for a RfD.

The NRC Committee conducted dose-response modeling, and concluded that in-utero exposure to MeHg resulting in a cord blood mercury level of 58 : g/l (corresponding to a maternal hair level of about 12 ppm) would be associated with a doubling of the percent of children performing at the lowest 5% level on this test. The NRC also examined the potential confounding and/or interaction of PCB exposure with MeHg exposure in the Faroes study. The dose-response relationship between MeHg and performance was no different among subgroups with low and high PCB exposure. Thus, whether or not PCB influenced performance, there was an independent effect of MeHg.

The report recommended that this blood concentration, converted to mean maternal MeHg dose (: g/kg/day), be divided by an uncertainty factor adjustment of 2-3 to account for population variability in the conversion to an intake dose. An additional uncertainty factor to account for other health effects such as cardiovascular, immunotoxic, and delayed neurological effects, which may be occurring at lower levels of exposure, was also recommended. The report concluded that an overall uncertainty factor adjustment of "at least 10" was appropriate. This gives a maternal hair concentration which is essentially equivalent to that underlying the existing US EPA RfD (11 ppm), and applying an equivalent uncertainty factor adjustment (10) based, albeit, on somewhat different rationale, would result in an RfD that is quantitatively unchanged from that derived from the Iraqi poisoning (0.1 : g/kg/day).

Based on review of the NRC report (NRC 2000) as well as the NIEHS report, and on additional independent review, the US EPA has recently re-affirmed its former RfD of 0.1 µg/kg/day, albeit supported by new data and a new rationale. In 1999, the ATSDR derived a Minimal Risk Level (MRL) value - essentially equivalent to an RfD - for MeHg of 0.3 : g/kg/day based primarily on the absence of observed effect in the Seychelles study, and only indirectly addressing the positive findings from the Faroe Islands. These values are not very far apart and given the remaining uncertainties, it is likely that the lower value will be protective of most children.

5. Other Studies

The neurologic and neurobehavioral effects of mercury on children and adults have been studied in other areas, although seldom with a complete prospective design.

In their pilot study of Peruvian neonates born to mothers with a range of MeHg values up to 30 ppm in hair, Marsh et al. (1995) performed neurologic examinations and inquired about developmental landmarks in a sample of 110 mother-infant pairs. They provide only P values on correlations, rather than actual mercury or correlation levels. Although they consider their study negative, there are suggestive positive correlations (p values of 0.10-0.13), particularly in females, suggesting delayed development.

Neurobehavioral effects have been more clearly demonstrated in Amazonian Indians with high fish consumption and elevated mercury (Lebel et al. 1998). These results were considered influential by the National Research Council (NRC 2000) in conjunction with the Faroe Island results.

6. Summary and Conclusions: Methylmercury Neurodevelopmental Toxicity

It is clear that MeHg is a neurotoxin, which can cause a range of developmental abnormalities in children exposed *in-utero*. The critical question for assessing the impact of mercury on human health is whether, within the range of exposure associated with consumption of sport and commercial fish, there is a significant risk of adverse effects. Although historical and ongoing studies have not produced a clear-cut and unambiguous answer to this question, there are credible scientific data, which suggest that at some currently encountered levels of fish consumption, significant risks can occur. These risks relate to subtle and population-based deficits in developmental performance, mostly within the range of "normal" performance. It appears that the current US EPA RfD for protection against such adverse effects, 0.1 : g/kg/day, is appropriate and protective. Additional data from ongoing studies may further clarify this picture, but it is likely that uncertainties will remain for the foreseeable future.

C. Methylmercury Adult Toxicity

The adult toxicity of MeHg has been characterized largely through studies of the poisoning episodes in Japan, and Iraq (ATSDR 1999a; US EPA 1997e; WHO 1990). These studies revealed a continuum of effects on the central nervous system, including death, but extending through (in order of decreasing threshold of effect) ataxia (lack of motor coordination), dysarthria (difficulty in speech), deafness, and paraesthesia (numbness or tingling characteristically in the lips and extremities). The onset of these effects, even at high doses, characteristically has a long latency period of weeks to months. Dose-response modeling for paraesthesia as the most sensitive (critical) toxic effect from the several populations, and studies yielded good agreement in terms of the threshold for occurrence. A LOAEL (lowest-observed-adverse-effect-level) dose estimate of 3.0 : g/kg/day was identified. This dose approximately corresponds to a hair mercury concentration of 50 ppm. The US EPA applied an uncertainty adjustment of 10 to the LOAEL to estimate the NOAEL (no-observed-adverse-effect-level) to derive a RfD (Reference Dose) of 0.3 : g /kg/day. No uncertainty adjustment was used to address other common uncertainties (e.g., sensitive sub-populations).

This RfD was officially adopted by the US EPA in 1985. It was officially superseded by the current US EPA RfD of 0.1 : g/kg/day, which specifically addresses in utero developmental effects. Because the current (developmental) RfD is lower than the previous RfD, it is considered to be protective of all segments of the population. The US EPA has not, however, revised the assumptions or conclusions underlying the former RfD to provide guidance for protection of adults from health effects of MeHg. As such, it might be applied to consideration of safe exposure to MeHg by male adults, and adolescents, and women who are not pregnant or planning pregnancy within a year. This value (0.3 : g/kg/day) forms the basis for the current NJ Department of Environmental Protection's advisories for fish consumption for MeHg for the "general" population (Toxics in Biota Committee 1994).

Since the adoption of the former (i.e., "adult") MeHg RfD by the US EPA in 1985, additional information on the non-developmental toxicity of MeHg has become available. Some of this information suggests that the basis for the "adult" RfD may not address more subtle neurological effects of MeHg, and/or may not be protective against non-neurological effects of MeHg. Kosatsky and Foran (1996) have pointed out several weaknesses in studies of potential MeHg effects in adults with hair concentrations below 50 ppm. They suggest that these weaknesses call into question the ability of those studies to identify possible effects at levels below those identified as the basis of the "adult" RfD. Among these weaknesses is the

concentration on more obvious and clinical manifestations of MeHg toxicity (e.g., paraesthesia) to the general exclusion of more subtle (e.g., performance-based) endpoints. For example, long-term follow-up of the population exposed to MeHg in Minamata, Japan (Harada 1995; Kinjo et al. 1993) indicates worsening of MeHg effects (including more subtle subjective complaints) with aging.

There also appears to be uncovering of latent effects with aging among those previously asymptomatic. The worsening and/or uncovering of effects with aging was not addressed in the dose-response assessment for the "adult" RfD. Studies in the Brazilian Amazon of populations consuming MeHg contaminated fish (without direct exposure to mercury use in gold mining) suggest neurotoxic effects including: deficits in visual contrast and color discrimination; visual field constriction; and disorganized movement with increasing MeHg exposure in adults with hair mercury concentrations below 50 ppm (Lebel et al. 1998; Lebel et al. 1996). As these individuals may have been exposed starting in utero however, these observations may also reflect developmental effects of MeHg. In eastern Finland adult men have both elevated fish consumption and high mortality from coronary heart disease. Controlling for other risk factors, Salonen et al. (1995) found that the risk of coronary heart disease, cardiovascular disease, and acute myocardial infarction increased with mercury exposure from fish consumption. The risk of an acute myocardial infarction doubled, and the risk of death from cardiovascular disease increased 2.9 fold for a hair mercury level of 2.0 ppm compared to background levels. This is a lower level of exposure than that associated with adverse neurological developmental effects (see previous section). Although further confirmation of such associations is needed, such findings suggest that the current "adult" RfD for MeHg may not be adequate for protection against more subtle neurologic effects than those originally considered, and/or may not address the most critical endpoints of "adult" MeHg toxicity.

The recent NRC (2000) report recommended that while an RfD for methylmercury should be based on neurological developmental effects, uncertainty factor adjustments should be applied that address the potential occurrence of non-developmental effects such as cardiovascular and immunotoxicological effects at doses lower than those protective against neurological developmental effects. The implication of such an RfD is that it would be protective against both developmental and non-developmental (i.e., adult effects of methylmercury). The US EPA adopted an RfD in July 2001 that addresses "adult" effects. Such an RfD logically precludes the application of the former "adult RfD".

The former US EPA RfD for MeHg (0.3 μg/kg/day) was based on clinical neurological effects observed in adults. While this value has been superceded by the current RfD for developmental effects, it continues to be used to address the non-childbearing portion of the population. Current evidence suggests that more subtle neurological effects and/or non-neurological effects of MeHg may not be addressed by this "adult" RfD. Research, specifically addressing the potential for adverse effects at lower levels of exposure than those addressed by the "adult" RfD, should be undertaken.

D. Toxicology of Inorganic Mercury

1. Introduction

The toxicology of inorganic mercury can be divided into separate categories of mercury salts (essentially Hg^{++}) and elemental mercury vapors (Hg^0). At exposure levels likely to be encountered in the environment, the target organs and critical health endpoints for each form are somewhat different, and can be considered separately. This report presents only a brief summary of the toxicology of these species of inorganic mercury. Although the mercury in

the atmosphere is predominantly the inorganic form, it occurs at concentrations generally far below those of health concern. Thus, most aspects of inorganic mercury toxicity were beyond the scope of the Task Force. Further information and a guide to more detailed sources can be found in the ATSDR Toxicological Profile for Mercury (ATSDR 1999a), and kidney toxicity has been reviewed by Zallups (1997).

2. Ionic Mercury and Mercury Salts (Hg^{++})

Absorption of the salts of Hg^{++} by ingestion varies by their solubility. Inorganic mercury absorption ($HgCl_2$) increases at alkaline pH, and the mercury compounds are transported bound to high molecular weight proteins (Endo et al. 1986). In adults, about 15% of an oral dose of mercuric chloride ($HgCl_2$) are absorbed. However, young animals absorb a larger fraction of the ingested dose, and this is presumably true of children as well. The most common form of Hg^{++} in the environment is mercuric sulfide (HgS) which has low solubility and is very poorly absorbed. In the body the highest concentrations of Hg^{++} are found in the liver and kidney. Hg^{++} does not readily cross either the blood-brain barrier or the placenta. The kidney appears to be the most sensitive organ to Hg^{++} exposure. Although degeneration and atrophy of the renal tubular epithelium resulting in kidney dysfunction are characteristic, mercury also damages the renal glomerulus through an autoimmune reaction resulting in albuminuria. This effect is the basis for the current US EPA reference dose (RfD) for Hg^{++} of 0.3 : g/kg/day, based on $HgCl_2$. The extent to which this value is applicable to health effects in humans is not clear since it was derived from exposure of a strain of rat known to be sensitive to auto-immune glomerular effects. Its applicability appears to be based on the assumption that this test system is likely to predict effects in sensitive humans.

3. Elemental Mercury (Hg^0)

Hg^0 is very poorly absorbed by ingestion or dermal contact. However, Hg^0 is a liquid at room temperature with a relatively high vapor pressure which yields mercury vapor which is readily absorbed in the lung and results in its significant potential for toxicity. Elemental mercury that is inhaled is either exhaled, retained in the upper or lower respiratory tract, or absorbed into the circulation. A variety of studies reviewed by Leggett et al. (2001) indicate that only about 20% of inhaled mercury is exhaled. They estimate a three-order absorption with about 56% of the inhaled mercury absorbed into the blood very rapidly and 87% absorbed within hours and the remainder within days. Hg^0 absorbed into the blood from the lungs can cross both the placental and blood-brain barriers. In most organs, Hg^0 is metabolized relatively rapidly to Hg^{++}. Long-term inhalation exposure can lead to Hg^{++} accumulation in the kidneys. The brain, however, is the critical organ for Hg^0 toxicity. Hg^{++} is also formed from Hg^0 in the brain. It is not clear whether it is the initially deposited Hg^0, or its metabolite, Hg^{++}, which is the ultimate source of toxicity.

Acute inhalation of high levels of Hg^0 vapor (e.g., due to heating of metallic Hg) can result in death from asphyxiation, lung edema, and necrosis of lung tissue. Long-term exposure to lower levels can result in frank neurological effects such as tremor, personality changes, depression, difficulty sleeping, memory loss, etc. This suite of effects has long been known as erethism, characterized by emotional lability with alternating shyness and combativeness. The critical effects with chronic exposure to much lower levels of Hg^0 vapor are fine tremors and slight reductions in coordination. A recent study of dentists exposed over long periods to Hg^0 in the preparation and installation of amalgam fillings reported subtle changes in tests of neurological performance. The current US EPA Reference Concentration (RfC) for Hg^0 of 0.3 Fg/m^3 is based on fine tremors and memory disturbances observed in studies of occupational exposure. Currently the potential for exposure to Hg^0 in the NJ population is from cultural/folk uses of mercury, from dental amalgams, and from indoor spills of Hg^0

resulting from breakage of thermometers or mercury-containing instruments (e.g., barometers).

4. Summary and Conclusions: Toxicology of Inorganic Mercury

Salts of inorganic mercury primarily affect the kidney, but are not well absorbed. Elemental mercury primarily affects the central nervous system, and is well absorbed by inhalation, but not by ingestion. Subtle neurological effects may occur with even low levels of exposure, making elemental mercury in residences resulting from spills and intentional use potentially dangerous.

E. Recommendations

Reduce exposures from cultural uses of mercury. To accomplish this, NJ should:

1. **Complete research and evaluate available data on cultural uses and associated exposures.**
2. **Provide outreach and education materials to communities and health professionals.**
3. **Develop and implement appropriate legislation and regulations that limit the sale of elemental mercury, except for medical and other approved uses, reflecting the NEWMOA model legislation.**

(From Recommendation "J.1, J.2 and J.3" in Volume 1)

The federal government and, to the extent possible, the State of NJ should pursue research to elucidate the extent of exposure of the population to elemental mercury from dental amalgams and from cultural/folk uses. Research should also address the potential for combined developmental and/or adult toxicity from joint exposures to methylmercury and elemental mercury.

The federal government should pursue the human health-based objectives of the US EPA's Mercury Research Strategy to clarify the significant remaining uncertainties in the neurodevelopmental toxicology of methylmercury.